UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/069,034	08/05/2002	Preeti G. Lal	PF-0731 USN	9342

27904 7590 12/23/2004

INCYTE CORPORATION
EXPERIMENTAL STATION
ROUTE 141 & HENRY CLAY ROAD
BLDG. E336
WILMINGTON, DE 19880

EXAMINER	
BUNNER, BRIDGET E	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 12/23/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/069,034	LAL ET AL.	
	Examiner	Art Unit	
	Bridget E. Bunner	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 October 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-30* is/are pending in the application.

4a) Of the above claim(s) *8,10,15 and 18-28* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7,9,11-14,16,17,29 and 30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-30* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of Application, Amendments and/or Claims

The amendment of 07 October 2004 has been entered in full. Claims 1-2, 5, 7, 11-13, and 17 are amended. Claims 29-30 are added.

This application contains claims 8, 10, 15, and 18-28 drawn to an invention nonelected with traverse in the communication of 23 April 2004. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1-7, 9, 11-14, 16-17, and 29-30 are under consideration in the instant application.

Withdrawn Objections and/or Rejections

1. The objections to the specification at pg 4 of the previous Office Action (07 July 2004) are *withdrawn* in view of the amended title and specification (07 October 2004).

2. The objection to claims 1-2, 5, 11, and 17 at pg 4 of the previous Office Action (07 July 2004) is *withdrawn* in view of the amended claims (07 October 2004).

3. The rejections of claims 13-14 at pg 16-17 of the previous Office Action (07 July 2004) are *withdrawn in part* in view of the amended claim (07 October 2004). Please see 35 U.S.C. § 112, second paragraph, below.

4. The rejection of claim 12 under 35 U.S.C. § 102(a) as set forth at pg 17-18 of the previous Office Action (07 July 2004) is *withdrawn* in view of the amended claim (07 October 2004).

Claim Rejections - 35 USC § 101 and 35 USC § 112, first paragraph

5. Claims 1-7, 9, 11-14, 16-17, and 29-30 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a credible, specific, or substantial asserted utility or a well established utility. Novel biological molecules lack established utility and must undergo extensive experimentation. The basis for this rejection is set forth for claims 1-7, 9, 11-14, 16-17 at pg 4-10 of the previous Office Action (07 July 2004).

Claims 1-2 and 16-17 are directed to an isolated polypeptide comprising an amino acid sequence selected from the group consisting of : a) an amino acid sequence consisting of SEQ ID NO: 28, b) an amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 28, c) a biologically active fragment of the amino acid sequence of SEQ ID NO: 28, and d) an immunogenic fragment of the amino acid sequence of SEQ ID NO: 28. Claims 3-6 and 11 recite an isolated polynucleotide encoding a polypeptide, an isolated polynucleotide consisting of SEQ ID NO: 65, and a polynucleotide sequence having at least 90% sequence identity to the polynucleotide of SEQ ID NO: 65. Claims 7 and 9 recite a recombinant cell transformed with the recombinant polynucleotide and a method for producing a polypeptide. Claim 12 recites an isolated polynucleotide comprising at least 150 contiguous nucleotides of SEQ ID NO: 65. Claims 13-14 are directed to a method for detecting a target polynucleotide in a sample. Claim 29 recites an isolated polypeptide comprising an amino acid sequence having at least 95% sequence identity to SEQ ID NO: 28. Claim 30 recites an isolated polynucleotide sequence having at least 95% sequence identity to SEQ ID NO: 65.

Applicant's arguments (07 October 2004), as they pertain to the rejections have been fully considered but are not deemed to be persuasive for the following reasons.

(i) Applicant asserts that the proteins and sequences of the invention are useful in the diagnosis, treatment, and prevention of cell proliferative disorders, immune disorders, and inflammatory disorders (pg 36-38 of the specification).

Applicant's arguments have been fully considered but are not found to be persuasive. Specifically, as discussed in the previous Office Action, this asserted utility is not specific or substantial. The specification does not disclose specific disorders associated with a mutated, deleted, or translocated MEMAP polynucleotide (SEQ ID NO: 65) or polypeptide (SEQ ID NO: 28). Significant further experimentation would be required of the skilled artisan to identify individuals with such a disease. Further, the specification discloses nothing about the normal levels of expression of the polynucleotide or polypeptide. The altered or abnormal levels of the polynucleotide or polypeptide cannot be determined until a baseline control level is established. Since this asserted utility is also not present in mature form so that it could be readily used in real world sense, the asserted utility is not substantial. Although Applicant indicates that pg 37-38 of the specification provides examples of disorders or cancers that the claimed invention can be used to treat or prevent, these examples are simply a generic, non-specific list of cancers, diseases, and conditions. There is no disclosure in the specification teaching that the claimed MEMAP polypeptide and polynucleotide are associated with any of these disorders or cancers. Additionally, significant further research would have been required of the skilled artisan to determine whether the claimed MEMAP polypeptide or polynucleotide is overexpressed or underexpressed in any disorder or cancer to the extent that it could be used as a diagnostic or therapeutic, and thus the implicitly asserted utility is not substantial.

(ii) Applicant argues that according the sequence alignment of Exhibit 1, the protein of SEQ ID NO: 28 is 100% identical to BPIL1. Applicant indicates that the annotation of BPIL1 and associated post-filing date reference (Mulero et al., Immunogenetics 54: 293-300, 2002) (Exhibits 2-3) show that BPIL1 is a member of the lipid/transfer/lipopolysaccharide binding protein (LY/LBP) gene family and is related to the bactericidal/permeability-increasing protein (BPI). Applicant states that Mulero et al. describes BPIL1 as being downregulated in larynx carcinoma tissue. Applicant also indicates that Mulero et al. explains BPIL1 is overexpressed in inflamed disease tissues and that these genes "may play a role in innate immunological functions...in inflammation, host defense or pain" (pg 299). Applicant submits that because the invention has at least one substantial and credible utility as set forth in the specification and confirmed by Mulero et al., i.e. the treatment and/or prevention of larynx carcinoma, the rejection under 35 U.S.C. § 101 should be withdrawn.

Applicant's arguments have been fully considered but are not found to be persuasive. Specifically, the specification of the instant application only identifies the polypeptide of SEQ ID NO: 28 and the polynucleotide sequence of SEQ ID NO: 65 as a membrane associated protein (or MEMAP; see pg 5, lines 4-17). The specification does not teach any significance or functional characteristics of the MEMAP-28 polypeptide or polynucleotide. The specification does not teach that MEMAP-28 is a member of the lipid/transfer/lipopolysaccharide binding protein gene family or that it is related to the bactericidal/permeability-increasing protein (BPI). Instead, the specification discloses that MEMAP-28 has homology to a potential ligand (odorant) binding protein (see Table 2). Table 2 even discloses a putative olfactory ligand binding domain in the claimed polypeptide of SEQ ID NO: 28. Mulero et al. also teach that another human EST

with an identical sequence to BPIL1 was found to be downregulated in laryx carcinoma (pg 296, col 1). However, the specification of the instant application does teach that the claimed invention is down regulated in larynx carcinoma. Furthermore, Mulero et al. only examine the tissue expression of BPIL1. At pg 297-299, Mulero et al. disclose that the BPIL1 gene is expressed at low levels in normal tissue and upregulated in hypertrophic tonsils. However, the asserted utility of tissue typing for the claimed MEMAP-28 polypeptide and polynucleotide is not specific or substantial. Numerous unrelated nucleotide sequences would also show a similar tissue typing pattern. Also, evidence of mere expression in a tissue is not tantamount to a showing of a role in cell proliferative disorders, immune disorders, and inflammatory disorders.

Additionally, Mulero et al. do not teach any functional activity of the BPIL1 protein. Mulero et al. simply disclose that "the sequence similarity to the LT/LBP family suggests that the BPIL proteins likely perform similar functions in vivo. Their restricted pattern of expression, in particular their overexpression in inflamed disease tissues, suggests that these genes may play a role in innate immunological functions" (pg 299, col 1, 3rd full paragraph).

The assertion that the MEMAP-28 (BPIL1) has biological activities similar to a known LT/LBP family cannot be accepted in the absence of supporting evidence, because the relevant literature reports examples of polypeptide families wherein individual members have distinct, and sometimes even opposite, biological activities. For example, Tischer et al. (U.S. Patent 5,194,596) establishes that VEGF (a member of the PDGF, or platelet-derived growth factor, family) is mitogenic for vascular endothelial cells but not for vascular smooth muscle cells, which is opposite to the mitogenic activity of naturally occurring PDGF which is mitogenic for vascular smooth muscle cells but not for vascular endothelial cells (column 2, line 46 to column

3, line 2). The differences between PDGF and VEGF are also seen *in vivo*, wherein endothelial-pericyte associations in the eye are disrupted by intraocular administration of PDGF but accelerated by intraocular administration of VEGF (Benjamin et al., 1998, Development 125:1591-1598; see Abstract and pp. 1594-1596). In the transforming growth factor (TGF) family, Vukicevic et al. (1996, PNAS USA 93:9021-9026) disclose that OP-1, a member of the TGF-β family of proteins, has the ability to induce metanephrogenesis, whereas closely related TGF-β family members BMP-2 and TGF-β1 had no effect on metanephrogenesis under identical conditions (p. 9023, paragraph bridging columns 1-2). See also Massague, who reviews other members of the TGF-β family (1987, Cell 49:437-8, esp. p. 438, column 1, second full paragraph to the end). Similarly, PTH and PTHrP are two structurally closely related proteins which can have opposite effects on bone resorption (Pilbeam et al., 1993, Bone 14:717-720; see p. 717, second paragraph of Introduction). Finally, Kopchick et al. (U.S. Patent 5,350,836) disclose several antagonists of vertebrate growth hormone that differ from naturally occurring growth hormone by a single amino acid (column 2, lines 37-48).

Generally, the art acknowledges that function cannot be predicted based solely on structural similarity to a protein found in the sequence databases. For example, Skolnick et al. (2000, Trends in Biotech. 18:34-39) state that knowing the protein structure by itself is insufficient to annotate a number of functional classes, and is also insufficient for annotating the specific details of protein function (see Box 2, p. 36). Similarly, Bork (2000, Genome Research 10:398-400) states that the error rate of functional annotations in the sequence database is considerable, making it even more difficult to infer correct function from a structural comparison of a new sequence with a sequence database (see especially p. 399). Such concerns are also

echoed by Doerks et al. (1998, Trends in Genetics 14:248-250) who state that (1) functional information is only partially annotated in the database, ignoring multi functionality, resulting in underpredictions of functionality of a new protein and (2) overpredictions of functionality occur because structural similarity often does not necessarily coincide with functional similarity. Smith et al. (1997, Nature Biotechnology 15:1222-1223) remark that there are numerous cases in which proteins having very different functions share structural similarity due to evolution from a common ancestral gene. Brenner (1999, Trends in Genetics 15:132-133) argues that accurate inference of function from homology must be a difficult problem since, assuming there are only about 1000 major gene superfamilies in nature, then most homologs must have different molecular and cellular functions. Finally, Bork et al. (1996, Trends in Genetics 12:425-427) add that the software robots that assign functions to new proteins often assign a function to a whole new protein based on structural similarity of a small domain of the new protein to a small domain of a known protein. Such questionable interpretations are written into the sequence database and are then considered facts.

Therefore, based on the discussions above concerning the specific examples of structurally similar proteins that have different functions, along with the art's recognition that one cannot rely upon structural similarity alone to determine functionality, the specification fails to teach the skilled artisan how to use the claimed polynucleotides to make biologically active MEMAP-28 without resorting to undue experimentation to determine what the specific biological activities of the MEMAP-28 polypeptide are.

6. Claims 1-7, 9, 11-14, 16-17, and 29-30 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention. The basis for this rejection is set forth for claims 1-7, 9, 11-14, and 29-30 at pg 10 of the previous Office Action (07 July 2004).

Applicant's arguments (07 October 2004), as they pertain to the rejections have been fully considered but are not deemed to be persuasive for the following reasons.

Applicant states that a specific and substantial asserted utility, as described above. Specifically, since Applicant has not provided evidence to demonstrate that the MEMAP polynucleotide and polypeptide have a specific and substantial asserted utility or a well established utility, one skilled in the art would not know how to use the claimed invention.

6a. Furthermore, claims 1-7, 9, 11-14, 16-17, and 29-30 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicant's arguments (07 October 2004), as they pertain to the rejections have been fully considered but are not deemed to be persuasive for the following reasons.

(i) Applicant argues that Table 2 of the instant specification discloses potential phosphorylation sites, potential glycosylation sites, a signal peptide domain, a transmembrane domain, membrane glycoprotein signature sequences, and an olfactory ligand binding domain of

SEQ ID NO: 28. Applicant contends that one of ordinary skill in the art would know how to make and use biologically active fragments of SEQ ID NO: 28 by referring to Table 2 of the specification.

Applicant's arguments have been fully considered but are not found to be persuasive. The broad brush discussion of making and screening for variants at pg 26-30 of the specification does not constitute a disclosure of a representative number of members. No such variants of the polypeptide of SEQ ID NO: 28 or the polynucleotide of SEQ ID NO: 65 were generated or shown to have activity. Although the specification (Table 2) identifies *putative* glycosylation sites, and signature sequences, motifs, and domains in the polypeptide of SEQ ID NO: 28, the specification does not teach whether or not every domain is essential for protein function or if specific amino acids within the domains are essential for protein function. The specification does not disclose if any other specific regions or amino acids of the polypeptide sequence are required for protein function. The specification's general discussion of making and screening for variants constitutes an invitation to experiment by trial and error. Such experimentation is considered undue. Additionally, as was found in Ex parte Hitzeman, 9 USPQ2d 1821 (BPAI 1987), a single embodiment may provide broad enablement in cases involving predictable factors such as mechanical or electrical elements, but more will be required in cases that involve unpredictable factors such as most chemical reactions and physiological activity. See also In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970); Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 927 F.2d 1200, 1212, 18 USPQ2d 1016, 1026 (Fed. Cir.), cert. denied, 502 U.S. 856 (1991).

(ii) Regarding recitation of "an immunogenic fragment", Applicant asserts that that are not claiming any antibodies, whether specific or non-specific to SEQ ID NO: 28. Applicant submits that claim 1 merely recite an immunogenic fragment and that the specification need not teach one of skill in the art how to use non-specific antibodies.

Applicant's arguments have been fully considered but are not found to be persuasive. As discussed in the previous Office Action, the specification teaches the term "biologically active" refers to "a protein having a structural, regulatory, or biochemical functions of a naturally occurring molecule. (pg 13, lines 2-3). The specification also teaches that "an 'immunogenic fragment' is a polypeptide or oligopeptide fragment of MEMAP which is capable of eliciting an immune response when introduced into a living organism, for example, a mammal. The term 'immunogenic fragment' also includes any polypeptide or oligopeptide fragment of MEMAP which is useful in any of the antibody production methods..." (pg 19, lines 6-10). However, the specification does not enable the claimed biologically active or immunogenic fragments and variants of MEMAP. The specification does not disclose methods or working examples that show how to use "biologically active" fragments or that describe the specific activity associated with the fragments. An antigenic fragment of the amino acid sequence of SEQ ID NO: 28 gives rise to an antibody specific for SEQ ID NO: 28. However, an 'immunogenic fragment" of the amino acid sequence of SEQ ID NO: 28 gives rises to an antibody that is not specific for SEQ ID NO: 28. An "immunogenic fragment" elicits a general immune response. The specification provides little or no guidance indicating what specific immune response is generated by all possible fragments recited in the claims. Additionally, undue experimentation would be required by the skilled artisan to generate and screen all the fragments for any activity.

(iii) Applicant contends that one of skill in the art would be able to make a polypeptide and polynucleotide with a certain level of identity, i.e., 90% and 95% identity, to a reference sequence. Applicant argues that one of skill in the art would also be able to make a fragment having 60 (or 150) contiguous nucleotides of SEQ ID NO: 65. Applicant references Table 2. Applicant states that Table 2 discloses various structural characteristics of the claimed polypeptide, including potential glycosylation sites, and signature sequences, motifs, and domains.

Applicant's arguments have been fully considered but are not found to be persuasive. As discussed above, the broad brush discussion of making and screening for variants at pg 26-30 of the specification does not constitute a disclosure of a representative number of members. No such variants of the polypeptide of SEQ ID NO: 28 or the polynucleotide of SEQ ID NO: 65 were generated or shown to have activity. The specification's general discussion of making and screening for variants constitutes an invitation to experiment by trial and error. Such experimentation is considered undue. Furthermore, certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These or other regions may also be critical determinants of antigenicity. These regions can tolerate only relatively conservative substitutions or no substitutions (see Wells, 1990, Biochemistry 29:8509-8517; Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495). However, Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein and DNA which are

tolerant to change and the nature and extent of changes that can be made in these positions. Although the specification identifies *putative* glycosylation sites, and signature sequences, motifs, and domains in the polypeptide of SEQ ID NO: 28, the specification does not teach whether or not every domain is essential for protein function or if specific amino acids within the domains are essential for protein function.

7. Claims 16-17 are also directed to a composition comprising an effective amount of SEQ ID NO: 28 and variants thereof and a pharmaceutically acceptable excipient. However, the phrase "pharmaceutically acceptable excipient" in claims 16-17 recites an intended use of the MEMAP polypeptide for treatment or administration in an animal. The basis for this 35 USC § 112, first paragraph issue is set forth at pg 13 of the previous Office Action (07 July 2004).

Applicant's arguments (07 October 2004), as they pertain to the rejections have been fully considered but are not deemed to be persuasive for the following reasons.

Applicant asserts that one of ordinary skill in the art would be able to make and use the particular invention without undue experimentation. Applicant states that a "composition comprising an effective amount of a polypeptide of claim 1 and a pharmaceutically acceptable excipient" is supported in the specification. Applicant points out that claims 16-17 do not recite a method of use.

Applicant's arguments have been fully considered but are not found to be persuasive. Specifically, the word "pharmaceutically acceptable excipient" is interpreted by the Examiner as the intended use of the composition for treatment or administration in an animal, and thus the specification has to be examined with respect to the sole intended use. The specification does

not teach how to use a MEMAP polypeptide without undue experimentation for the treatment of a disease in an animal. There are no working examples directed to a particular disorder in an animal or administration of any MEMAP, particularly the polypeptide of SEQ ID NO: 28, to an animal for treatment. The specification does not teach any working examples that demonstrate administration of the MEMAP of SEQ ID NO: 28 to any animal for the treatment of any disorder or disease. One skilled in the art would not know how to use the invention of the instant application because the invention is highly complex and a large quantity of experimentation is necessary to determine the proper dosage, route of administration, and appropriate patient population for any "pharmaceutical" composition, especially the MEMAP-28 polypeptide. In the instant case, there is a low guidance level in the specification and an absence of working examples. Additionally, the effects of the administration of a "pharmaceutical" composition comprising MEMAP of SEQ ID NO: 28 are unpredictable in subjects. (Note, this issue could be overcome by deleting the word "pharmaceutically acceptable excipient" from the claims.)

Proper analysis of the Wands factors was provided in the previous Office Action. Due to the large quantity of experimentation necessary to determine the specific activity of a polypeptide fragment and to how to use immunogenic fragments, to determine an activity or property of the disclosed polypeptide such that it can be determined how to use the claimed polynucleotides encoding MEMAP-28, to generate the infinite number of derivatives recited in the claims and possibly screen same for activity, and to determine the quantity of MEMAP polypeptide to be administered, the most effective administration route, and the duration of the treatment; the lack of direction/guidance presented in the specification regarding same; the absence of working examples directed to same; the complex nature of the invention; the

unpredictability of the effects of the MEMAP polypeptide *in vivo* and the state of the prior art establishing the unpredictability of the effects of mutation on protein structure and function; and the breadth of the claims which fail to recite particular biological activities and also embrace a broad class of structural fragments and variants, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

8. Claims 1-7, 9, 11-14, 16-17, and 29-30 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The basis for this rejection is set forth for claims 1-7, 9, 11-14, and 16-17 at pg 14-16 of the previous Office Action (07 July 2004).

The claims are directed to an isolated polypeptide comprising an amino acid sequence selected from the group consisting of : a) an amino acid sequence having at least 90% or 95% sequence identity to the amino acid sequence of SEQ ID NO: 28, b) a biologically active fragment of the amino acid sequence of SEQ ID NO: 28, and c) an immunogenic fragment of the amino acid sequence of SEQ ID NO: 28. The claims also recite an isolated polynucleotide that encodes the polypeptides above and a polynucleotide sequence having at least 90% or 95% sequence identity to the polynucleotide of SEQ ID NO: 65. The claims recite an isolated polynucleotide comprising at least 150 contiguous nucleotides of SEQ ID NO: 65.

Applicant's arguments (07 October 2004), as they pertain to the rejections have been fully considered but are not deemed to be persuasive for the following reasons.

(i) Applicant asserts that Table 2 discloses various structural characteristics of the claimed invention, including potential phosphorylation sites, potential glycosylation sites, a signal peptide domain, a transmembrane domain, membrane glycoprotein signature sequences, and an olfactory ligand binding domain of SEQ ID NO: 28. Applicant contends that one of ordinary skill in the art would be able to create functionally equivalent 90% identical polypeptide and polynucleotide variants by following the teachings of the specification. Applicant indicates that by using the information from Table 2, one of ordinary skill in the art would know to retain those portions of the sequence identified in Table 2 when creating a variant 90% identical to SEQ ID NOs: 28 and 65. Applicant argues that with respect to claim 12, the specification does provide adequate written description for a polynucleotide comprising at least 60 contiguous nucleotides of SEQ ID NO: 65.

Applicant's arguments have been fully considered but are not found to be persuasive because the Applicant has not provided evidence to demonstrate that the skilled artisan would be able to envision the infinite number of polypeptides and polynucleotides recited in the claims. The detailed structure of one MEMAP-28 polynucleotide and polypeptide in the specification of the instant application is not a representative number of embodiments to support the description of an entire genus of functionally equivalent polynucleotides and polypeptides which incorporate all fragments and mutants, derivatives, and variants having at least 90% or 95% sequence identity to the amino acid sequence of SEQ ID NO: 28, at least 90% or 95% sequence identity to the polynucleotide of SEQ ID NO: 65, or at least 150 contiguous nucleotides of the polynucleotide of SEQ ID NO: 65. Therefore, only an isolated polynucleotide consisting of the nucleic acid sequence of SEQ ID NO: 65, an isolated polynucleotide encoding the polypeptide of

SEQ ID NO: 28, and an isolated polypeptide consisting of the amino acid sequence of SEQ ID NO:28, but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph. Furthermore, the broad brush discussion of making or screening for fragments and variants does not constitute a disclosure of a representative number of members. No such variants were made or shown to have activity. Only one member, MEMAP-28 of SEQ ID NO: 28, is disclosed. The specification's general discussion of making and screening for variants constitutes an invitation to experiment by trial and error. Such does not constitute an adequate written description for the claimed variants.

Furthermore, to provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of compete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only factor present in the claims is a partial structure in the form of a recitation of percent identity and polynucleotide/polypeptide fragments and variants. There is not even identification of any particular portion of the structure that must be conserved. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus. Although the specification (Table 2) identifies *putative* glycosylation sites, and signature sequences, motifs, and domains in the polypeptide of SEQ ID NO: 28, the specification does not teach whether or not every domain is essential for protein function or if specific amino acids within the domains are essential for

protein function. The specification does not disclose if any other specific regions or amino acids of the polypeptide sequence are required for protein function.

35 USC § 112, second paragraph

9. Claims 13-14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

10. The term "specifically hybridizes" in claim 13, line 5 is a relative term which renders the claimed indefinite. The term "specifically hybridizes" is not defined by the claims, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Neither the specification nor the art provide unambiguous definitions for "hybridizes" and "specifically hybridizes". Therefore, the metes and bounds of the claims cannot be determined by one skilled in the art. The basis for this rejection is set forth at pg 16-17 of the previous Office Action (07 July 2004).

Applicant's arguments (07 October 2004), as they pertain to the rejections have been fully considered but are not deemed to be persuasive for the following reasons.

Applicant respectfully disagrees with the Examiner, but has amended claim 13 to recite clear hybridization conditions. Applicant's arguments and claim amendment have been fully considered but are not found to be persuasive. Although claim 13 now recites clear hybridization wash conditions, the term "specifically hybridizes" is still a relative term which renders the claims indefinite. For example, it is not clear to the Examiner or one skilled in the art the difference between "hybridizes" and "specifically hybridizes". The metes and bounds of the

claims cannot be determined. (Please note that this issue could be overcome by amending claim 13 to recite, for example, "...and which probe hybridizes at wash conditions...".)

Conclusion

No claims are allowable.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bridget E. Bunner whose telephone number is (571) 272-0881. The examiner can normally be reached on 8:30-4:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached on (571) 272-0961. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Elizabeth C. Kemmerer

BEB
Art Unit 1647
17 December 2004

ELIZABETH KEMMERER
PRIMARY EXAMINER